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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/818,461	03/27/2001	Benjamin D. Silverman	YOR920000779US2	1831

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EXAMINER	
BORIN, MICHAEL L	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 10/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/818,461	SILVERMAN, BENJAMIN D.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/31/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *7-21, 28-32,39-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,22-27 and 33-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/05/06 has been entered.

Status of the claims

2. Amendment filed 06/05/06 is entered. Claims 1-43 are pending. Claims 7-21, 28-32,39-43 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected groups.

As for election of species requirement, applicant elected species wherein adjusted second order moment of hydrophobicity is determined. Inasmuch as prior art does not teach second order moment of hydrophobicity to be used for determining if a protein is globular, previously withdrawn claims 4,25,36 are included into consideration. Claims 1-6,22-27,33-38 are under examination.

Claim Rejections - 35 USC § 112, first paragraph.

3. Claims 1-3,6,22-24,27,33-35,38 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for determining whether a protein is globular using zero- or second-order moment of hydrophobicity as addressed in claims 4,5, does not reasonably provide enablement for a method of determining whether protein is globular using shifted hydrophobicity distribution as addressed in general in claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

With respect to determining whether a query protein is globular, specification teaches how to use second-order moment of hydrophobicity (p. 5, lines 5-15):

The shape or profile of the adjusted second-order moment can be used to determine if a protein is globular. All globular proteins studied to date exhibit a characteristic profile such that the adjusted second-order moment rises from zero to a high positive value, then passes through zero and becomes strongly negative. There is generally only one zero crossing after the high positive value, and the profile becomes strongly negative after the zero crossing. Any protein that does not exhibit this profile most likely is not a globular protein.

Further, with respect to use of zero- or second order moments specification teaches (p. 5, bottom):

For all globular proteins, both peaks of the zero- and second-order moments occur at the same distance from the centroid of the protein. Globular proteins tend to exhibit a certain range of these distance ratios. If a protein or decoy has a hydrophobicity ratio that is not within the range, then the protein or decoy is likely not a globular protein. (p. 5, bottom)

However, specification does not teach how to determine whether protein is globular by merely using "shifted hydrophobicity" as addressed in claim 1.

As stated in the previously discussed reference of Karplus, using hydrophobicity values in general is unpredictable:

> Over the years, numerous "hydrophobicity scales" and "solvation parameters" have been proposed based on both theoretical considerations and ΔG transfer measurements... Differences among such scales have fueled an active debate regarding which values, if any, are the ones that are relevant for protein folding, and led some to abandon the paradigm of hydrophobicity in favor of the more absolute concept of hydration

In view of the above, it is the Examiners position that with the insufficient guidance and working examples and in view of unpredictability and the state of art one skilled in the art could not make and/or use the invention with the claimed breadth without an undue amount of experimentation.

4. Claims 1-4,6,22-25,27,33-36,38 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for determining a "spatial" hydrophobicity distribution based on second order moment of hydrophobicity, does not reasonably provide enablement for a method of determining "spatial" distribution using shifted distribution in general (i.e., as in claim 1) or zero-order moment of hydrophobicity (as in claim 4).

Hydrophobicity is determined based merely on amino acid sequence does not provide "spatial" information. As described in specification, each residue is assigned a hydrophobicity value "h" , and zero-order moment is H0 is a sum of such hydrophobicities (p. 6-7). Unlike first- or second-order moments of hydrophobicity which include distance "r" between centroids of residues and centroid of protein, hydrophobicity value "h" or zero-order moment do not contain "spatial" information.

Consequently, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim Rejections - 35 USC § 103 .

5. Claims 1,6,22,27,33,38 are rejected under 35 U.S.C. 103(a) as unpatentable over Eisenberg et al. (Faraday Symposia of the Chemical Society, 1982, 17, 109-120).

The claims are directed to method of determining if a protein is a globular protein by determining spatial hydrophobicity distribution of a protein, shifting the hydrophobicity accounting for average hydrophobicity and comparing the shifted hydrophobicity of a query and globular protein.

Eisenberg et al describes determination of hydrophobicity distribution in proteins. The reference teaches determining hydrophobicity as a hydrophobic dipole momemnt (i.e., determining spatial hydrophobicity), shifting the hydrophobicity accounting for average hydrophobicity [see equation (3)] and comparing the shifted hydrophobicity for various proteins. Although the reference is not directed specifically to determining whether a proteinh is globular (as in instant claims) it teaches that globular proteins has a particular pattern of dipole hydrophobic moments (see pages 115-116) and that quadruple hydrophobic moment indicates when a protein is globular (see abstract, end of first paragraph). Thus, it would be obvious to one skilled in the art that comparing hydrophobic moments can indicate whether a protein is globular. One would be motivated to use such comparison as a tool for spatial profiling a query protein.

With respect to claims 22,27,33,38, the review article of Eisenberg does not specify the way calculations have been made. However, providing an automatic means to replace a manual activity which accomplished the same result is not sufficient to distinguish over the prior art.

6. Claims 1,3,6,22,24,27,33,35,38 are rejected under 35 U.S.C. 103(a) as unpatentable over Cornette et al. (J. Mol. Biol., 1987,195,659-685) in view of Eisenberg et al. (Faraday Symposia of the Chemical Society, 1982, 17, 109-120).

Cornette teaches calculation of hydrophobic moment for each residue (*cf.* claim 6*)* - i.e., determining "hydrophobicity distribution" - and plotting them on a graph. See p. 660, right column through p. 661, left column, and Fig. 2. Fig. 2 presents "normalized intensity" i.e., values which are based on the "difference between values of hydrophobicity and average hydrophobicity. For comparative purposes, to compare different approaches, the hydrophobicity values are normalized (*cf.* claim 3*)* to have a value of 1000 at the frequency angle of 100° (i.e., "hydrophobicity distribution" is "shifted").

With respect to claims 22,24,27,33,35,38, the method of Cornette is computer-assisted and thus involves computer medium and computer system.

Cornette does not teach using hydrophobicity estimates to determine whether a protein is globular. Eisenberg teaches that various hydrophobicity estimates demonstrate that

globular proteins has a particular pattern of hydrophobicity (see rejection over Eisenberg, above). Thus, as it would be obvious to one skilled in the art to use presentation of hydrophobicity described in Cornette to be used to compare structural patterns in different proteins, and because Eisenberg indicates that various estimates of hydrophobicity demonstrate particular patterns for globular proteins, one would be motivated to use hydrophobiic moments as described in Cornette as a tool for determining whether of protein of interest has a globular structure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael Borin, Ph.D.
Primary Examiner
Art Unit 1631

mlb
10/10/2006